Review Article

Body Mass Index, Blood Pressure and Lipid profile in type 2 diabetes-Review

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ABSTRACT

Diabetes mellitus type II (formerly noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is a metabolic disorder that is characterized by hyperglycemia (high blood sugar) in the context of insulin resistance and relative lack of insulin. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease (although this is not the case in people of East-Asian ancestry).

Key Words: Type 2 diabetes, Obesity, Anthropometry, Lipid profile

INTRODUCTION

Diabetes mellitus (DM) is a syndrome of impaired carbohydrate, fat and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin. Type I DM is also called as insulin dependent diabetes mellitus (IDDM) is caused by lack of insulin secretion.

Type II DM is also called as non insulin dependent diabetes mellitus (NIDDM) is initially caused decreased sensitivity of target tissues to metabolic effects of insulin. This reduced insulin sensitivity of insulin is often called as Insulin resistance[1]. Type II DM is the most common type of diabetes and usually associated with obesity. It usually develops after the age 40[2].

The incidence of type II diabetes mellitus (Type II DM) is rapidly increasing worldwide and it constitutes a major health problem in both developed and developing countries[3]. There is a great deal of evidence that both genetic and environmental factors are of importance in the pathogenesis of Type II DM. Obesity, in particular the central obesity, physical inactivity, and a diet rich in saturated fatty acids increases the risk of type II DM[4].

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with type II DM having 2 to 4 times higher risk of developing CVD when compared to non diabetics. In diabetics cardiovascular complication occurs at an earlier age and often results in premature deaths[5].

Patients with type II DM are frequently affected by atherosclerotic vascular disease. Multiple factors contribute to this accelerated atherosclerosis in type II DM. These factors include dyslipidemia, obesity, hypertension, and insulin resistance[6-9].

Lipid abnormalities are more common in type II DM and are aggravated with poor glycaemic control. The classical dyslipidemia in type II DM is so called atherogenic dyslipidemia. This is a constellation of lipid abnormalities which includes increased serum triglycerides (TG), increased low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) also known as "lipid triad"[10].

Lipid abnormalities play an important role in the causation of diabetic atherosclerosis. Elevated levels of TG, cholesterol, and LDL-C increases the risk of atherogenesis and high levels of HDL-C in contrast bear an inverse relationship to the risk of atherosclerosis and coronary heart disease (CHD)[11-12].

Type II DM is associated with centralized and disharmonious distribution of fat. There is a significant association

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between regional fat distribution and CVD risk factors. Abdominal or central adiposity is considered the most important determinant of CVD and Type II DM[13]. Although imaging techniques can accurately determine total body fat and its distribution in human but are not suitable for use in large population studies because of cost, irradiation exposure, and limited availability[14].

The use of simple anthropometric measurements seems to diagnose obesity in early stages due to its benefits in routine monitoring and assessment in patients. Some of the simple anthropometric measures used routinely includes Body mass index (BMI), Waist circumference (WC), Waist to hip ratio (WHR) [15, 16].

BMI is widely used for classification of obesity, but it does not account for the variations of fat distributions. Waist circumference is the best simple anthropometric index of abdominal visceral adipose tissue and also the best index for predicting CVD risks[17].

In India 50% of diabetics has hypertension (HTN).The frequency of hypertension in diabetic population is almost twice as compared to non-diabetic general population[7]. In hypertensive patient with DM, atherosclerosis gets accelerated and its consequences get manifested earlier[18]. Both HTN and type II DM are recognised as independent CVD risk factors[19].

These risk factors have a great potential for prevention through modification of life style and dietary changes.

REVIEW OF LITERATURE

Type II DM is due to insulin resistance or reduced insulin sensitivity, combined with relatively reduced insulin secretion. There is a great deal of evidence that both genetic and environmental factors are of importance in the pathogenesis of Type II DM. Whereas the genetic factors are still poorly understood, numerous studies have shown that obesity (in particular, abdominal obesity), physical inactivity, a high-fat diet, and a diet rich in saturated fatty acids increases the risk of diabetes[4]. It is a chronic disease that requires long-term medical attention both to limit the development of its devastating complications and to manage them when they do occur.

Insulin resistance associated with obesity is induced by adipokinase, free fatty acids and chronic inflammation in adipose tissue. The pancreatic beta cells compensate for insulin resistance by hypersecretion of insulin. However, at some point beta cell compensation is followed by beta cell failure and diabetes ensues[20] **(Fig. 1).**
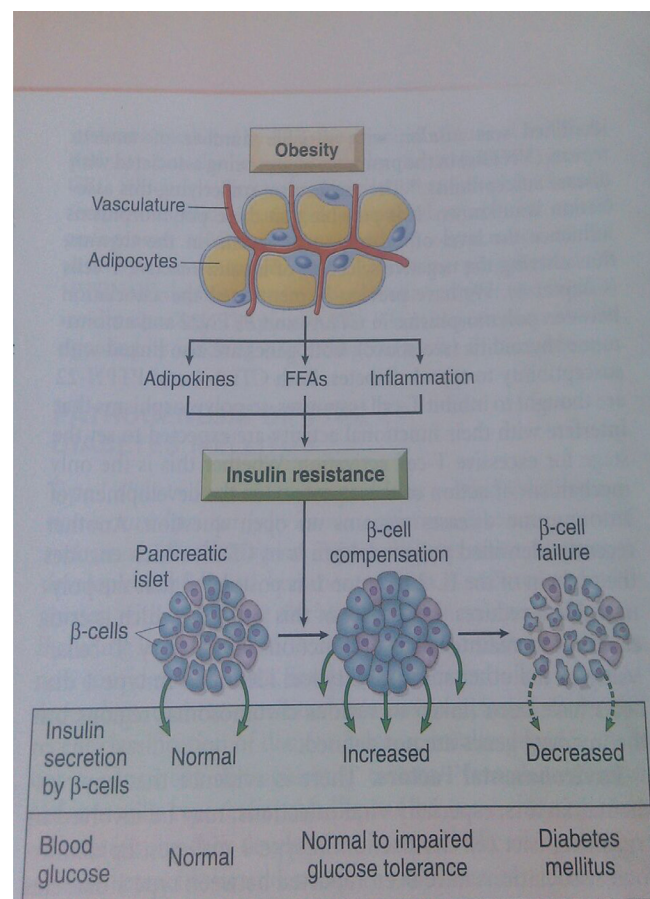

Figure 1: Showing basic mechanism of Insulin resistance and Type II diabetes.

The classic symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss. Other symptoms that are commonly present at diagnosis include a history of blurred vision, itchiness, peripheral neuropathy, recurrent vaginal infections, and fatigue. Many people, however, have no symptoms during the first few years and are diagnosed on routine testing. People with type II diabetes mellitus may rarely present with hyperosmolar hyperglycaemic state (a condition of very high blood sugar associated with a decreased level of consciousness and there is a great low blood pressure) **(Fig 2)**[4].
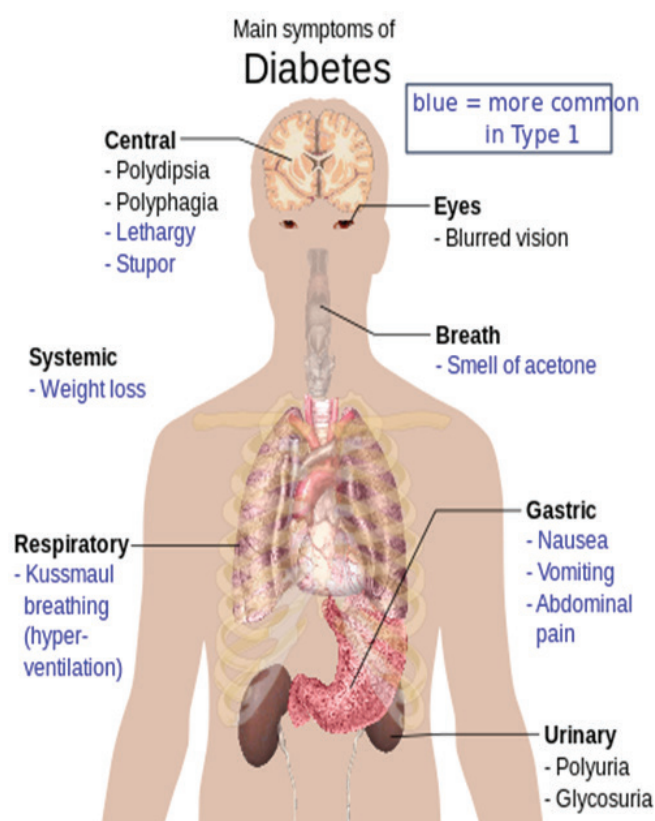
Figure 2: Showing signs and Symptoms of type II Diabetes.

World health organization (WHO) has predicted that India would experience the largest increase (48% increase in total population and 168% increase in population with >65 years of age) in type II DM and would have the greatest number of diabetic individuals in the world by the year 2030 (31.7 million in 2000 to 79.4 million in 2030) [21, 22].

CVD is the most prevalent complication of DM[23]. The age-adjusted cardiovascular mortality is at least 2-fold higher in diabetic men than in non-diabetic subjects in the presence of many numbers of major risk factors[24]. The survival after myocardial infarction is worse in diabetic men and women[25].

In general population, women experiences relative protection from myocardial infarction and usually develop coronary artery disease (CAD) approximately 10 years later than men but diabetes blunts the cardiovascular benefits of female gender[26].

The incidence of death from cardiovascular causes in diabetic subjects without a history of myocardial infarction during a 7-year follow-up was similar to the incidence observed in non-diabetic subjects with a history of myocardial infarction [27].

Coronary angiography is one of the most reliable procedures adopted to diagnose CAD and angiographic data on Indian patients with suspected CAD had revealed that triple vessel disease (TVD) was much higher in diabetes as compared to non-diabetics [28].

These observations highlight the high prevalence of undiagnosed CVD in type II DM and the gravity of cardiovascular events in this population. The problem of undiagnosed disease is the result of lack of awareness by the patients of the strong association between diabetes and CVD. Multiple factors contribute to the accelerated atherosclerosis in diabetes. These factors include excess prevalence of risks such as dyslipidemia and advanced glycosylated end products, obesity, hypertension, and, the state of insulin resistance[29] (Fig. 3).
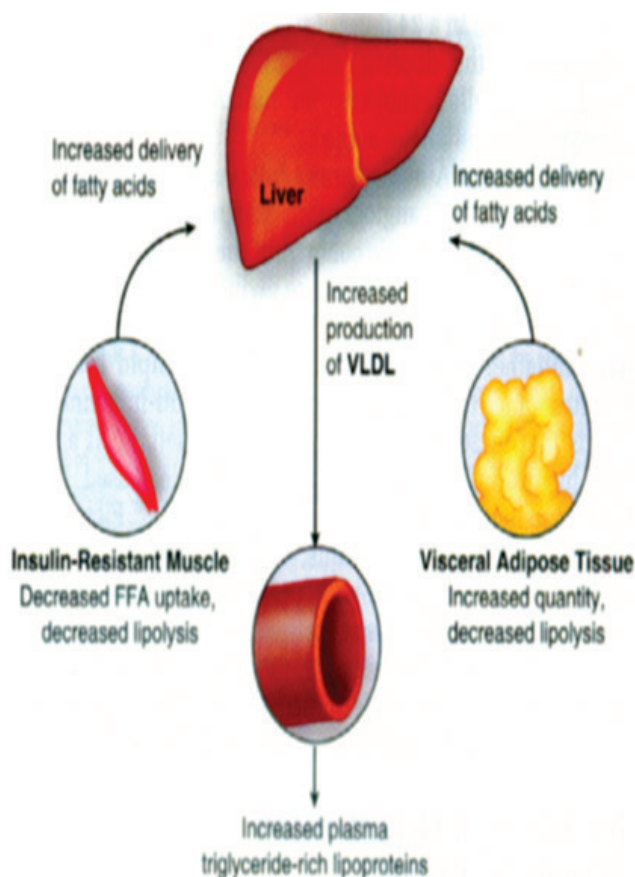

Figure 3: Pathogenesis of dyslipidemia[31].

In type II DM there is a global dysfunction of **lipoprotein metabolism**. There is increased delivery of free fatty acids (FFA) to liver due to excess adipose efflux and impaired skeletal muscle uptake increases hepatic production of very low density lipoprotein (VLDL) and cholesterol ester synthesis. Over production of triglyceride- rich lipoproteins and impaired clearance by lipoprotein lipase leads to hypertriglyceridemia in diabetes[30]. Triglyceride level tends to vary inversely with HDL levels as cholesterol ester transfer protein mediates exchange of cholesterol from HDL to VLDL.

The combination of elevated triglycerides and low HDL is more common than elevated total and LDL cholesterol in diabetic patients with CAD. Increased concentration of small, dense LDL in diabetic person results from abnormal cholesterol and triglyceride transfer between VLDL, and

LDL and depends on increased levels of VLDL, particularly when triglyceride concentration are higher than 130mg/dl[31].

Small dense LDL-C is proatherogenic, first LDL-C moves into sub endothelium and is oxidized by macrophages and smooth muscle cells (stage 1 and 2). Release of growth factors cytokines attracts additional monocytes (stage 3 and 4). Foam cell accumulation and proliferation results in growth of the plaque (stage 6, 7, and8) [20, 32] **(Fig.4)**.
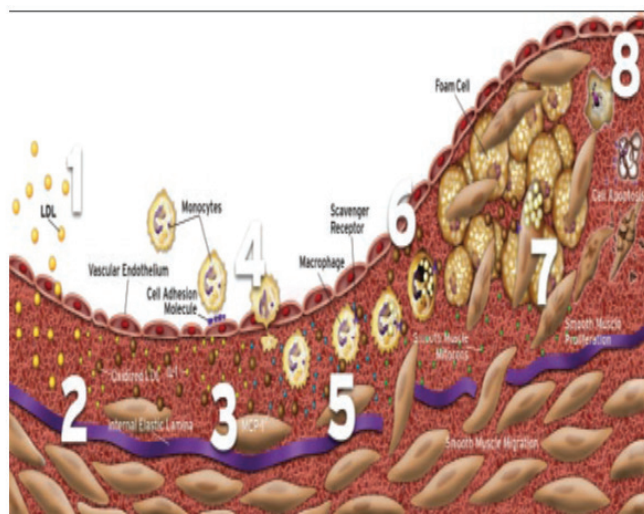

Figure 4: Showing 7 stages of development of an atherosclerotic plaque[33].

Atherosclerosis is the process underlying CVD, which includes coronary heart disease (CHD), myocardial infarction (MI), ischemic stroke, and peripheral vascular disease (PVD) [34]. Atherosclerosis is the primary cause of death in patients with type II DM and it seems to be closely related to a specific cluster of lipid abnormalities, including low levels of HDL-C, increased numbers of small dense LDL-C, and elevated triglyceride levels[11].

The classical dyslipidemia in type II DM is so called atherogenic dyslipidemia. This is a constellation of lipid abnormalities also known as "lipid triad" [10]. This risk is even greater when the lipid triad is accompanied by insulin resistance, a procoagulant state, and hypertension—a condition known as the cardiovascular dysmetabolic syndrome. Each of these abnormalities is associated with an increased risk for cardiovascular morbidity and mortality.

Majority of Indian type II DM are dyslipidemic at baseline. The most common pattern of dyslipidemia is high LDL-C and low HDL-C among both males and females contributing to 22.7% and 33% patients of diabetic dyslipidemia, respectively[35, 36].

The most prevalent problem among males is high LDL –C while among females low HDL –C emerged as a bigger threat. In Indian subjects with DM the lipid profile and pattern is greatly influenced by the ethnic origin, food habit, nutritional status and lifestyle influences. There has been a quantum increase in the incidence of CAD amongst urbanites while the picture in rural India has changed very little, suggesting the major impact of lifestyle modifications on lipid profiles and the deleterious effect of the latter in causing accelerated and more extensive CAD as evident angiographically[37].

Hypercholesterolemia, hypertriglyceridemia, elevated LDL-C, and low HDL-C are generally accepted as strong risk factors for cardiovascular disease (CVD) and mortality[38-40].

Several evidence has contributed to our current understanding of the relationship between increase in plasma cholesterol and development of CHD. Premature atherosclerosis results from high cholesterol levels, even in the absence of other cardiovascular risk factors. Large population surveys have shown that plasma cholesterol level is predictive of CHD[41]. In the Framingham study individuals below 50 years, cholesterol level was directly related to cardiovascular mortality. The study highlights the profound effects of lipoprotein abnormalities on incidence of CAD in diabetics compared to non diabetics[42].

In a large prospective study, over 350,000 men aged 35 to 57 years were followed for 6 years. A curvilinear relationship between plasma cholesterol and coronary death rate was observed. If a risk ratio of 1 is assigned for a cholesterol level of 200 mg/dl, then at 250 mg/dl, the risk is doubled. This relation between cholesterol and CHD is not lost in the presence of other risk factors such as diabetes. The presence of diabetes further increased the risk of a given cholesterol level[43]. Because most cholesterol in plasma is transported in LDL and this is responsible for the correlation between plasma cholesterol and CHD. On the contrary some studies showed no significant difference in the lipids and lipoprotein profiles of diabetics and that of control [5].

High-density lipoprotein cholesterol has been repeatedly shown to be an independent inverse predictor of CVD risk in epidemiological and observational studies, and patients with low HDL-C levels have been suggested to have a comparable CVD risk as those with high LDL-C levels[44,45]. The distribution of HDL-C levels varies with age, sex, race, and education. Women have higher levels of HDL-C than men.

Alcohol consumption is directly related to HDL-C levels and an inverse relation between smoking and HDL-C levels has been reported. Low HDL-C represents a highly prevalent and potentially modifiable risk factor for CVD prevention in type II DM[46, 47].

The rise in triglyceride rich lipoprotein concentrations which normally occur after a fat containing meal is found to be greater in type II DM patients than in people without diabetes[48].

Exaggerated postprandial spikes in glucose and lipid levels can lead to an excess of free radicals and trigger a cascade of endothelial dysfunction and sympathetic hyperactivity- this state is known as postprandial dysmetabolism, is an independent predictor of CVD[49, 50].

In particular, these patients are characterized by an increased and prolonged postprandial response of both intestine- and liver-produced lipoproteins, especially of their remnant particles, which have been proven highly atherogenic[32]. Type II DM patients with very good blood glucose control and low fasting plasma triglyceride levels, well below 150 mg/dl, was indicated as optimal to reduce cardiovascular risk in diabetic patients[51].

Some studies showed that postprandial lipid abnormalities is present only in the type II diabetic patients with fasting hypertriglyceridemia (serum triglycerides, >150 mg/dl)[52, 53]. Studies done on patients with established acute myocardial infarction (AMI) with or without diabetes showed serum triglyceride level to be higher in diabetic groups whereas other lipid fraction were nearly similar and not significantly elevated. Also studies done on siblings of patients with CAD showed existing dyslipidemia in the sibling as compared to healthy[28].

Epidemiological evidence linking total plasma triglycerides to CVD risk has been the subject of much debate. Studies conducted on diabetic patients with and without CAD after an oral vitamin A fast load test showed no difference in metabolism of post prandial lipoproteins in both groups and is not related to coronary artery disease[54]. In a similar study conducted on diabetic patients with and without CAD by measuring post prandial triglycerides showed no association with coronary artery disease[55].

The role of LDL-C in the development of CVD cannot be overemphasized as there is documented evidence that high level of LDL-C not only causes atherosclerosis but pharmacological interventions that reduce LDL-C cholesterol are associated with stabilization and regression of atherosclerosis in proportion to the cholesterol lowering achieved[56].

A problem with LDL-C and HDL-C, from a laboratory point of view, is that there is no widely accepted international standard for LDL-C and HDL-C. This makes it hard to compare assays performed at different laboratories, and it limits the possibility to transfer target values for these analyses from one country to another. Apolipoproteins are important components of lipoprotein particles, and there is accumulating evidence that measurement of various forms of apolipoproteins may improve the prediction of the risk of cardiovascular disease. ApoB, which indicates the number of potentially atherogenic lipoprotein particles, and apoA-I, which reflects anti-atherogenic HDL-C particles, may be additional lipid-related variables that more accurately indicate CVD risk than LDL-C[57-59].

Obesity has become a major worldwide epidemic affecting more than 300 million people, with changing food habits and increasing sedentary lifestyles, the prevalence of obesity has increased markedly[3]. Both absolute total fat and adipose tissue distribution are closely associated hyperlipidemia and CVD[60].

Although overweight and obesity are associated with an increase risk of type II DM and CVD, the pattern of fat distribution is also important in risk stratification. Intra-abdominal (visceral) fat deposition is linked to an increased risk for developing DM and CVD compared with a more peripheral (subcutaneous) fat distribution[61].

However, it remains uncertain which pattern of obesity is more significant predictor of metabolic syndrome. Many studies discovered that fat distribution, rather than absolute total fat, is more closely associated with these risk factors[60]. Other studies however, found that total body fat, rather than its distribution, is strong predictor of metabolic risk[62].

Adipose tissue is now viewed as an active endocrine organ and not merely as energy depots. The visceral adipose tissue (VAT) accounts for approximately 15% of total body fat in lean subject and includes the intraperitoneal (mesenteric and omental) fat, which drains into the portal circulation and retroperitoneal fat, which drains into the systemic circulation.

The aetiology of increased cardio metabolic risk in patients with increased VAT is not known, but there are many theories. The VAT is more insulin resistant, fuelling the hyperlipolytic state and worsening of insulin resistance. The increase in VAT mass possibly reflects the lack of capacity of subcutaneous tissue to store the energy excess that accumulates in liver, muscle, and pancreas, worsening insulin resistance[63].

Numerous cytokines are secreted from adipose tissue, including proinflammatory molecules such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α). Plasma levels of C-reactive protein (CPR), an inflammatory factor produced by liver and known to correlate with atherosclerosis, are increased in patients with visceral obesity[64]. It has been recently shown that the adipose tissue is infiltrated by macrophages contributing to inflammatory processes. Adiponectin, a protein derived from the adipose tissue, is known to improve insulin sensitivity and may protect against atherosclerosis. Adiponectin levels are decreased in obesity and in viscerally obese patients[65].

Another contributing factor may be local generation of cortisone due to increased activity of 11β-hydroxysteroid dehydrogenase in the VAT, which may further increase fat deposition, worsen insulin resistance, and increase cardio metabolic risks[66].

There are many ways to measure total body fat; traditionally, the gold standard for estimation has been hydro densitometry

(underwater weighing), based on the fact that fat tissue is less dense than muscle and bone. Other methods used to assess total body fat Dual–energy x-ray absortiometry (DXA) and body-fat distribution using computed tomography (CT) and magnetic resonance imaging (MRI) in humans are not suitable for use in large population studies because of cost, irradiation exposure, and limited availability, they are generally not appropriate outside specific research setting[14].

The use of simple anthropometric measurements seems to diagnose obesity in early stages. As a result, many attempts have been made to find out the most appropriate anthropometric index in different studies.

BMI or Quetelet index, defined as weight/height^2 is the most widely used and simple measure of body size, and frequently used to estimate the prevalence of obesity within a population. A BMI $\geq$ 25 Kg/m2 is associated with increased morbidity, primarily from DM and CVD, while a BMI >30 Kg/m2 is associated with increased risk for both morbidity and mortality, the latter mainly from diabetes, coronary heart disease (CHD), and stroke.

Rationale use of BMI is that it is supposed to closely correlate with tissue density, which in turn closely correlates with percent fat in body tissue (adiposity) obesity indices. An implicit assumption made in many epidemiologic analyses is that BMI alone is a sufficient measure of anthropometric effects. This is not necessarily true, however; whether BMI alone adequately captures the effect of anthropometric variables on health outcomes depends on many factors.

In particular, although BMI may capture most of the information on the body composition contained in weight and height, it does not capture information on body size. Also in a muscular patients may have high BMIs but low fat mass, and in elderly, BMI may underestimate fat mass due to decrease in lean body mass[67].

Body fat distribution is an important risk factor for obesity related disease. Increased visceral adipose tissue (also called central or abdominal fat) is associated with increased risk for cardio metabolic disease. Clinical evidence suggests that the association of diabetes with central obesity is stronger than the association with general fat. Studies using computed tomography and magnetic resonance imaging have provided further evidence to support that central obesity, visceral adipose tissue, and upper-body nonvisceral fat are the major contributors to the metabolic complication[68]. Central obesity has been associated with decreased glucose tolerance, alteration in glucose insulin homeostasis, reduced metabolic clearance of insulin, and decreased insulin-stimulated glucose disposal[69].

Waist Circumference is used as a surrogate marker of abdominal fat mass. WC correlates with subcutaneous and visceral fat mass and is related to increased cardio metabolic

risks. The National Heart, Lung and Blood Institute (NHLBI) recommended measuring WC along with BMI to assess patients risk stratification in subjects with a BMI between 25 and 35 Kg/m^2. Cut off points of WC that define higher risk for men and women based on ethnicity have been proposed by International Diabetes federation (IDF).

Some studies have proposed that WC is a superior indicator, because it requires only one measurement and is a better indicator of visceral fat and CVD risk[14]. There is a growing opinion that WC should be considered as a 'vital sign' and recorded in the same manner as weight and height in the medical chart of every patient. Also WC could replace both BMI and WHR as a simple indicator of need for weight management as a health promotion activity [70].

Waist-to-hip ratio (WHR) is a common anthropometric index used to assess abdominal obesity. The WHO included a high WHR defined as a ratio > 0.9 in men and 0.85 in women as a criterion for diagnosing the metabolic risks. A higher WHR has been associated with increased cardiovascular and DM risk[71]. Some studies found that WHR is more accurate tool to diagnose patients with a higher CVD risk compared with WC and BMI, whereas other studies have found a better correlation of cardio metabolic risks with WC compared with WHR[14]. WC provides a crude index of absolute amount of adipose tissue whereas WHR provides an index of relative accumulation of abdominal fat to generalized obesity [72].

More than three decades ago Harry Keen pinpointed two "bad companions" to diabetes: high blood glucose concentrations and high blood pressure, both associated with microalbuminuria[73]. HTN is a very common co morbid condition in diabetes and accounts for up to 85% of excess CVD risk. Patients with hypertension are more prone to diabetes than are normotensive patients. When HTN coexist with diabetes, the risk of development of CVD is doubled[3].

In type II DM, HTN usually clusters with the other components of cardio metabolic syndrome, such as central obesity, insulin resistance, dyslipidemia, hypercoagulation, increased inflammation and hyperuricemia.HTN in individuals with diabetes has characteristic features, including volume expansion, increased salt sensitivity, isolated systolic hypertension, loss of nocturnal dipping of blood pressure, increased propensity towards orthostatic hypotension and albuminuria.

The association between HTN and insulin resistance, and the resultant hyperinsulinemia is well established. In untreated patients with essential HTN, fasting and postprandial insulin levels were higher than in normotensive controls. Sensitively to dietary salt intake is greatest in elderly and diabetics, this is particularly important to consider in the management of HTN in patients with diabetes.

Patients with diabetes have loss of nocturnal dipping of blood pressure (BP), as demonstrated by 24 hour ambulatory

monitoring of BP. This is particularly important since loss of nocturnal dipping conveys excessive risk for stroke and myocardial infarction. With the progression of atherosclerosis in patients with diabetes, the larger arteries lose elasticity and become rigid.

The systolic blood pressure (SBP) increases disproportionately because the arterial system is incapable of expansion for any given volume of blood ejected from the left ventricle, leading to isolated systolic HTN[3]. Also there is a progressive increase in the prevalence of elevated blood pressure with adipose tissue[74, 75].

Metabolic syndrome consists of a cluster of risk factors strongly associated with an increased risk for atherosclerotic cardiovascular disease and type II DM [76]. The metabolic risk factors consist of a specific pattern of hyperlipidemia (elevated serum levels of triglycerides and apolipoprotein B, small LDL-C, and low levels of serum HDL-C), elevated BP, elevated plasma glucose concentration, a proinflammatory state, and a prothrombotic state[77, 78].

Central obesity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between WC and increasing adiposity. The diagnostic criteria for metabolic syndrome that could be easily implemented in clinical practice. These criteria include WC, blood pressure measurements, and serum levels of triglycerides, HDL-C, and fasting glucose[4].

CONCLUSIONS

- Type II DM often coexists with dyslipidemia, hypertension and obesity particularly abdominal obesity and simultaneously increases the risk of development of CVD.
- Also in the present study BMI and WC had a positive correlation with total cholesterol, triglycerides, LDL-C, VLDL, FBS, and BP and negative correlation with HDL-C.
- Thus simple anthropometric measures like BMI and WC can independently contribute to the prediction of risk factors of CVD and can be routinely used to identify those at risk
- Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy.

This is partly due to a number of complications with which it is associated, including: two to four times the risk of cardiovascular disease, including ischemic heart disease and stroke; a 20-fold increase in lower limb amputations, and increased rates of hospitalizations.

In the developed world, and increasingly elsewhere, type 2 diabetes is the largest cause of nontraumatic blindness and kidney failure. It has also been associated with an increased risk of cognitive dysfunction and dementia through disease processes such as Alzheimer's disease and vascular demen-

tia. Other complications include acanthosis nigricans, sexual dysfunction, and frequent infections.

So, Efforts should be made to continuously educate the populace on diabetics, its management, feeding and lifestyles. Diabetes is spreading like an epidemic all over the world. As is wisely said "prevention is better than cure" we need cautious evaluation of various risk factors so that appropriate measures can be taken timely, in order to prevent grave consequences.

The Lifestyle modifications, inclusive of dietary modification, regular physical activity and weight reduction are indicated for prevention of diabetes.

Low fat diet, daily exercise and lifestyle modification along with healthy weight reduction programme significantly reduces the incidence of type II diabetes mellitus, thereby preventing morbidity and or mortality related to the disease and its grave complications.

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